Parental Advisory: Maternal and Paternal Stress Can Impact Offspring Neurodevelopment

Jennifer C Chan, Bridget M. Nugent, and Tracy L. Bale

ABSTRACT
Parental stress exposures are implicated in the risk for offspring neurodevelopmental and neuropsychiatric disorders, prompting critical examination of preconception and prenatal periods as vulnerable to environmental insults such as stress. Evidence from human studies and animal models demonstrates the influence that both maternal and paternal stress exposures have in changing the course of offspring brain development. Mechanistic examination of modes of intergenerational transmission of exposure during pregnancy has pointed to alterations in placental signaling, including changes in inflammatory, nutrient-sensing, and epigenetic pathways. Transmission of preconception paternal stress exposure is associated with changes in epigenetic marks in sperm, with a primary focus on the reprogramming of DNA methylation, histone posttranslational modifications, and small noncoding RNAs. In this review, we discuss evidence supporting the important contribution of intergenerational parental stress in offspring neurodevelopment and disease risk, and the currently known epigenetic mechanisms underlying this transmission.

Keywords: Epigenetics, Intergenerational transmission, Placenta, PTSD, Sperm, Stress

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Early life stress is a well-established risk factor for neuropsychiatric disorders across the lifespan. Stress encompasses various environmental challenges that disrupt organismal homeostasis and result in physiological and/or behavioral responses (1). In humans, stressors can include metabolic challenges (e.g., famine), immune challenges (e.g., illness), and perceived psychological threats (e.g., social/emotional distress). In preclinical animal studies, stress can be imparted using psychological and/or physical challenges, including immobilization, social defeat, and isolation (2). During pregnancy, maternal stress alters the maternal milieu, which can directly or indirectly impact fetal development (3,4). Because the impact of stress is transmitted from parent to offspring, the term “intergenerational transmission” has been applied (5). However, preconception stress in either parent can impact germ cells, thus influencing development in one or more generations, resulting in transgenerational effects (6,7). As the most recent studies focusing on germ cell epigenetic transmission have been largely examined in paternal models, we discuss these studies in detail regarding stress programming of sperm as causal in offspring phenotypes.

Understanding the mechanisms by which parental stress exposure is ultimately communicated to the developing offspring brain is critical for elucidating the etiology of mental health disorders. Epigenetic control of gene expression, including DNA methylation, histone posttranslational modifications (PTMs), and noncoding RNAs, evolved to regulate and establish cell- and tissue-specific gene expression programs and to control normal cellular functions (8,9). Stress experienced during critical developmental windows when these epigenetic patterns are generated can result in reprogramming of cellular epigenomes, leading to long-term changes in patterns of gene expression and cellular function. More specifically, stress exposure can lead to such epigenetic alterations in sperm and oocytes, resulting in transmission of altered marks to the zygote (7). Following conception, stress exposure can also directly alter epigenetic programming of the fetus by disrupting the function of extraembryonic tissues, including the placenta, to promote alterations in key developmental signals throughout gestation. Thus, parental stress exposures during the preconception and prenatal windows can have lasting consequences on offspring development and, subsequently, adult outcomes (Figure 1).

In both human studies and animal models, intergenerational transmission of stress exposures has been associated with endophenotypes of stress-related neuropsychiatric disease in adult offspring, including disruption of the hypothalamic-pituitary-adrenal (HPA) stress axis. The HPA stress axis is important for glucocorticoid production in response to physiological and psychological challenges, and its dysregulation is an underlying feature of most neuropsychiatric disorders (10,11). Thus, many studies have focused on understanding developmental programming of the HPA stress axis as a readout of intergenerational transmission of stress exposure. In this review, we discuss the impact of maternal and paternal stress exposure on offspring neurodevelopmental outcomes, with a focus on offspring programming of the HPA stress axis. Moreover, we focus our discussion on the epigenetic mechanisms by which
intergenerational transmission of stress exposure may be signaled to developing offspring.

**MATERNAL MECHANISMS OF INTERGENERATIONAL STRESS TRANSMISSION**

Stress during pregnancy is associated with an increased risk for autism spectrum disorder, schizophrenia, affective disorders, and attention-deficit/hyperactivity disorder in offspring, largely related to the specific stage of pregnancy in which stress experience occurred (4). For instance, epidemiological and clinical studies report that early pregnancy, when epigenomic patterning is established, has the greatest impact on offspring brain development (12–16). Risk and outcome of stress exposure is also related to fetal sex, such that male offspring whose mothers experienced psychological stress during the first and second trimesters show an increased risk for schizophrenia and autism spectrum disorder (13–15), whereas female offspring exposed to high levels of cortisol during early pregnancy are at higher risk for affective disorders (16). Moreover, late gestation may be a sensitive period wherein stress exposure can lead to long-term alterations in cognitive function and risk for attention-deficit/hyperactivity disorder, particularly in female offspring (17–19). Although fetal development differs between species, rodent models of maternal stress exposure are valuable for elucidating the proximate mechanisms on programming offspring stress sensitivity. Our lab and others have shown that stress during early pregnancy has the greatest long-term impact on the offspring HPA stress axis, cognitive, and metabolic function, particularly in male offspring (20–25).

Numerous biological mechanisms converge to impart sex-specific alterations on offspring neurodevelopment following maternal stress, including effects on the maternal milieu, the placenta, and the developing fetus. While these factors have been explored for their contributions to offspring brain development, they are so tightly intertwined that alterations in one environment typically produce changes in the others. For instance, the placenta is a key source of corticotropin-releasing factor (CRF) (26), which feeds back to both the fetal and maternal pituitary (27,28). Placental CRF is critical for regulating the fetal HPA axis, and for proper production of glucocorticoids and androgens from the fetal adrenal gland (27,29). These steroids are necessary for organ maturation (30). Maternal stress enhances placental CRF production and signaling, which in turn modifies fetal HPA feedback and development (31). Rodent studies using treatment with the synthetic glucocorticoid dexamethasone during pregnancy demonstrate that potentiation of the maternal HPA axis reduces HPA axis sensitivity in adult offspring by attenuating the expression of glucocorticoid receptors (GRs) and mineralocorticoid receptors in the hippocampus, and enhancing anxiety-like behaviors and stress responsivity (32,33).

Similar to maternal stress, maternal infection during pregnancy is associated with an increased risk for autism spectrum disorder and schizophrenia, suggesting that these insults may have overlapping mechanisms that promote long-term changes in development (34–39). Interestingly, rodent models of maternal immune activation produce offspring phenotypes similar to those observed with maternal stress (40). Both maternal stress and infection promote an inflammatory state by increasing cytokine production during pregnancy, weakening the maternal immune system (41). In mice, signaling of the proinflammatory cytokine interleukin-6 is enhanced by both of these maternal insults, and inhibiting interleukin-6 signaling rescues the impact of maternal infection on offspring development (42,43). Prenatal stress exposure increases interleukin-6 specifically within the male placenta
and sensitizes the HPA stress axis and metabolic dysfunction in male offspring (44). Treatment of pregnant mice with a nonsteroidal anti-inflammatory drug during stress exposure ameliorates the programmatic dysfunction observed in male offspring, suggesting that maternal/fetal immune signaling mediates the effects of maternal stress exposure on placental and/or fetal brain development (44). Activation of the HPA axis is also known to interact with the maternal immune system, with glucocorticoids acting as important immunomodulators (45,46). For example, thymocytes, monocytes, and neutrophils express GRs, which mediate the transcriptional effects of glucocorticoids and can alter migration, differentiation, and proliferation (46,47). Clinical studies also report that psychosocial stress during pregnancy decreases lymphocyte activity (48). Other neuropeptide and neuroendocrine factors resulting from activation of the HPA axis can interact with immune cells as well, such as CRF regulation of mast cell degranulation (46,49). For a more comprehensive review on maternal immune regulation of fetal development, see Patterson (40) and Hsiao and Patterson (50).

**Placental Epigenetics and Neurodevelopmental Programming**

At the interface of maternal experience and the developing fetus lies the placenta, a tissue that serves as a gatekeeper of maternal signals, admitting critical nutrients and gasses from maternal circulation while blocking pathogenic intruders including viruses and bacteria (51). Here we focus our discussion on the evidence for epigenetic mechanisms in the placenta to promote sex-specific offspring responses to prenatal stress. For additional discussion on the involvement of the placenta in transmitting maternal signals to the developing fetal brain see previous reviews (51–54).

The fetally derived trophoblast lineage is the first to differentiate following fertilization, forming the outer blastocyst trophectoderm layer and eventually becoming the dominant cell type of the placenta (55). Male and female placentas express differences in gene expression, largely originating from the X and Y chromosomes (51,56). Of particular interest are the numerous X- and Y-linked genes that encode epigenetic machinery, including genes that affect the methylation status of the histone transcriptional repressor, H3K27, such as the histone demethylases, UTX and UTY, and the X-linked enzyme, O-linked N-acetylglucosamine transferase (OGT) (57). Differential expression of these and other broad epigenetic mediators are able to establish widespread sex differences in gene expression patterns within male and female trophoblast lineages (58). These sex differences may contribute to sex-specific susceptibility to prenatal perturbations, such as early prenatal stress, where male offspring are more vulnerable (59).

Evidence supporting this hypothesis has been demonstrated in rodents, wherein maternal stress significantly modifies placental gene expression and function in a sex-specific manner (56,60–62). We previously identified OGT as a placental mediator of the sex-specific effects of prenatal stress on HPA stress axis and metabolic programming (63). OGT is a nutrient-sensing enzyme that biochemically modifies thousands of proteins to promote widespread effects on cellular signaling, cell cycle regulation, proteosomal activity, transcriptional regulation, and additional critical cellular functions (for review see Bond and Hanover (64)). Further, OGT is a known mediator of epigenetic repression via its structural stabilization of the histone H3K27 methyltransferase, EZH2 (65–67), as well as epigenetic activation via its association with the ten-eleven translocation proteins at activational histone marks (68–70).

Female placental tissue (mouse and human) has nearly double the level of OGT as male tissue (60). In addition, placental OGT levels are reduced in response to early prenatal stress exposure in both male and female tissue. Might low levels of placental OGT be responsible for producing altered HPA function and endophenotypes of autism and schizophrenia in male offspring exposed to early prenatal stress? To test this hypothesis, we reduced OGT levels in placental trophoblasts in both sexes and found a recapitulation of the stress axis and metabolic dysregulation phenotype found previously only in male offspring (63). Thus, placental OGT activity appears to be a critical mediator of the sex-specific effects of prenatal stress exposure on offspring neurodevelopmental programming. However, as OGT targets myriad proteins and cellular processes, the downstream mechanisms involved in OGT’s sex-specific programming are still unknown.

**Maternal Preconception Stress**

Unlike the effects of paternal preconception stress, less is known about the mechanisms by which maternal preconception stress programs offspring outcomes. However, epidemiological evidence suggests that traumatic events before conception, such as childhood abuse and development of posttraumatic stress disorder, are associated with poor neuropsychiatric outcomes in offspring (71–73). Studies in children whose mothers survived the Holocaust suggest that one mechanism whereby maternal preconception stress may affect future generations is via alterations in DNA methylation of stress regulatory genes, such as FKBP5 and GR, which results in enhanced HPA stress axis sensitivity (73,74). Another recent study found that maternal childhood abuse correlates with greater placental CRF production during pregnancy (75), an intriguing finding that suggests integration of stress experience with the female reproductive tract. Further studies are needed to determine how traumatic preconception events alter maternal biology to allow for transmission to future generations.

**PATERNAL MECHANISMS OF INTERGENERATIONAL STRESS TRANSMISSION**

The number of studies examining the interaction of stress with the paternal germline to impact the programming of offspring development has grown in the last decade, with fascinating results implicating male life experiences in intergenerational transmission. The majority of epigenetic patterning of the male germ cell occurs prenatally, with some de novo DNA methylation and histone modifications occurring postnatally, before puberty [for review, see Ly et al. (76)]. During spermatogenesis, sperm histones are actively replaced by protamines, highly charged proteins that allow condensation of sperm chromatin to one tenth of that of somatic cells (77). As a result, mature sperm become transcriptionally inert and are considered
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resistant to external influences. However, recent studies have now turned the dogma upside down, demonstrating that mature sperm are responsive to homeostatic challenges, including dietary disruption, stress or trauma, and exposure to drugs of abuse, during the sperm maturation stage that occurs in the epididymis (78–82). In the following section we discuss the evidence from human studies and relevant animal models of intergenerational transmission of environmental perturbations through the paternal germline and the potential attributed epigenetic mechanisms. We focus on stress and trauma as these have been the most widely studied exposures in paternal transmission.

Human Studies and Animal Models of Paternal Stress

Retrospective epidemiological studies offer compelling evidence linking stress exposures during the male lifetime with disease risk in subsequent generations. Studies using birth measures and food supply records from the Swedish Famine in 1836 made the first claims for both intergenerational and transgenerational effects occurring through the male lineage. These studies established associations between food supply during early childhood in male offspring with altered health outcomes, including disease risk and longevity, in their sons and grandsons (83–85). Further, studies of a cohort of Holocaust survivors and their adult offspring found an increased prevalence of neuropsychiatric disorders, such as depression and posttraumatic stress disorder, and reduced cortisol levels and GR sensitivity in offspring whose fathers were survivors (74,86). Interestingly, as many of these children were conceived decades following the Holocaust, these outcomes support that traumatic stress promotes lasting effects through the paternal germline (74). Studies of male offspring exposed to chemicals from smoking, high-fat diets, and environmental toxicants also compared germ cell outcomes and reported associated epigenetic changes in sperm (87–89). Human studies investigating molecular signatures of stress in the male germline have not been completed but would provide valuable insight into novel mechanisms of intergenerational transmission resulting from paternal stress exposures.

Animal models of stress transmission via the paternal lineage provide a unique opportunity to identify germ cell epigenetic mechanisms without the major confounding factor of paternal behavior to consider. In most rodent models, male rodents do not participate in offspring rearing, allowing researchers to isolate the specific contribution of epigenetic changes in paternal germ cells. For example, in our studies, male mice breed with female mice for a maximum of 3 days and are removed from the female mouse’s cage immediately following observation of a copulation plug, significantly limiting the impact the stressed male mouse may directly have on maternal behavior or investment (79,90). Such studies have found that male mice exposed to chronic variable stress, dietary challenges, social defeat stress, and odor-paired fear conditioning have a number of altered epigenetic marks in their germ cells, including increased specific small noncoding RNA and changes in DNA methylation (78,79,82,91–93). Further, these altered epigenetic marks are associated with offspring behavioral, physiological, and metabolic outcomes characteristic of endophenotypes of stress-related neuropsychiatric disorders.

Interestingly, rodent studies have demonstrated germ cell susceptibility to stressful environments across the paternal lifespan. For instance, male mice exposed to maternal separation stress during the perinatal period sired offspring with depressive-like behaviors (94). Our lab has shown that male mice exposed to early prenatal stress present with altered stress coping behaviors and a heightened HPA stress response and transmit this phenotype only to their male, but not female, offspring in the next generation (95). These were two of the first rodent studies demonstrating that male germ cells can be reprogrammed by stress experience during early development. Sperm has distinct periods of differentiation, development, and maturation, and therefore the timing of stress exposure likely impacts distinct mechanisms (7). During the prenatal and perinatal periods, development and epigenetic patterning of germ cell precursors and the surrounding reproductive tissues is dynamic; therefore, stress exposure during these critical windows may disrupt the organization of important processes unique to this period (76).

Other studies examining paternal transmission have demonstrated that stress exposure of adolescent and adult animals alters germ cell programming. For example, male mice exposed to chronic variable stress sire male and female offspring that exhibit a significantly blunted HPA stress response, an endophenotype reflected in subsets of patients with major depressive disorder or posttraumatic stress disorder (96,97). Interestingly, this paternal effect occurred whether the sires were exposed to stress over the pubertal window or solely during adulthood, suggesting that stress exposures postpuberty (i.e., following maturation of the male reproductive system) evoke similar mechanisms. In contrast, retrospective studies from Swedish Famine cohorts associated nutritional challenge during preadolescence with changes in grandson longevity, while such challenges later in life produced no transgenerational effects (98). This disparity in the timing of germ cell vulnerability between our findings in stress-exposed rodents and the findings from the Swedish cohorts may be dependent on species, timing, or type of perturbation (e.g., psychosocial vs. nutritional). Therefore, further studies are needed to identify the windows of germ cell vulnerability in humans.

Stress Programming of Epigenetic Marks in Sperm

The observation that stress exposures across the male lifespan can lead to programming of offspring phenotypes has brought mounting attention to examination of epigenetic marks in sperm (99). Epigenetic marks have been described in mature sperm in both humans and rodents, including DNA methylation, histone PTMs, and small noncoding RNAs, and have been implicated in transmitting environmental information to the next generation (7,100). In this section, we discuss the evidence supporting the role of sperm epigenetic marks in the transmission and programming of offspring development following paternal stress exposures.

Sperm DNA methylation patterns are well described in normal germ cell development, and specific changes to these patterns have been reported in response to paternal stress exposure, such as maternal separation stress and odor-paired
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fear conditioning (91,94). During embryogenesis, the developing germ cell undergoes global erasure of DNA methylation marks. Following this process, de novo DNA methyltransferases specify germ cell methylation patterns that are distinct from those in somatic cells (76). An additional wave of active DNA demethylation of the paternal gamete occurs immediately postfertilization in the zygote (101). Importantly, some genomic loci are resistant to demethylation, a process of genomic imprinting critical for normal development, as mistakes at imprinted loci can result in neurodevelopmental disorders, including Angelman and Prader-Willi syndromes (102,103). Changes to sperm DNA methylation have been reported in rodent models of chronic stress experience (91,92,94). For example, male offspring that experienced odor-paired fear conditioning as adults had decreased DNA methylation at the specific genomic locus of the corresponding odor receptor in their sperm, suggesting a mechanism by which stress experience may produce offspring with specific behavioral changes (91). Intriguingly, in the same study, these sperm DNA methylation changes corresponded to increased offspring behavioral sensitivity to the associated odor. However, DNA methylation changes at this odor receptor were not present in the brains of these offspring, suggesting that sperm DNA methylation changes may influence other epigenetic mechanisms, such as histone PTMs, to program the offspring brain. In another study, male offspring exposed to maternal separation stress early in life sired offspring with depressive-like behaviors (94). These altered behaviors were also associated with changes in DNA methylation patterns at loci related to stress regulatory genes and epigenetic pathways in both the paternal germ cell and in the offspring brain. However, how stress induces such site-specific sperm methylation changes and how these changes influence the programming of adult offspring tissues to produce behavioral phenotypes are not known.

Despite the central dogma that mature sperm are transcriptionally inert, populations of small noncoding RNAs (~22–34 bp) have been well described in the mature sperm of humans and animals, including microRNAs (miRNAs), piwi-associating RNAs, and transfer RNA–derived fragments (tRFs) (104–107). Specifically, sperm miRNAs are critical for normal embryogenesis, where inhibition of sperm-borne miR-34c in the zygote resulted in zygotic arrest (108). In our study, male mouse chronic stress experience significantly increased 9 miRNAs in sire sperm (79). Remarkably, microinjection of these same 9 miRNAs into fertilized zygotes completely recapitulated the blunted HPA stress axis phenotype reported in our model of paternal stress, providing causal evidence for the role of stress-altered miRNAs in sperm (109). Other labs have corroborated the crucial role of stress-sensitive sperm miRNAs in programming offspring phenotypes via microinjection of total sperm RNA and tRF populations, a class of small noncoding RNAs derived from transfer RNAs (80,110,111). The mechanisms by which sperm small noncoding RNAs influence offspring neurodevelopment are not clear. Following zygote miRNA microinjection, we found a significant reduction of specific stored maternal messenger RNA populations at the 2-cell stage, supporting sperm miRNA canonical function in the embryo (109). Intriguingly, in this study, the two most repressed genes were Sirt1 and Ube3a, epigenetic regulators that have been associated with neurodevelopmental and metabolic disorders in humans (112,113). In another study, zygote microinjection of tRFs altered by paternal dietary challenge resulted in changes in zygote gene expression, in particular the repression of endogenous retroelements (111). Therefore, sperm small noncoding RNAs may alter critical genes during the preimplantation stages of embryogenesis, resulting in a cascade of cellular events that ultimately reprograms the offspring. Owing to the relative instability of RNA molecules compared with more long-lasting epigenetic marks, such as DNA methylation, it is unlikely that sperm-derived RNAs are maintained past early stages of embryogenesis, but rather produce a dynamic change in the developmental landscape, possibly additional epigenetic changes, that shapes the embryo trajectory.

Considering the exciting new evidence that sperm noncoding RNAs are changed by paternal perturbations and reprogram offspring development, mechanistic studies to determine how the male reproductive tract senses changes in the environment and alters sperm content are necessary before interventions can be considered. The source of RNA in mature sperm was previously assumed to be residual from spermatogenic processes (114). However, in the epididymis, the site of important posttesticular sperm maturation, a novel role of epithelial cell extracellular vesicles has recently been proposed in the delivery of small noncoding RNA to maturing sperm (115). For instance, the content of these “epididymosomes” was shown to alter sperm tRFs in response to paternal dietary challenge, supporting that epidydymal epithelial cells may be the dynamic mediators between paternal environmental exposures and sperm RNA changes (111).

Last, histone PTMs are also potential epigenetic signals in sperm. Roughly 1% of histones in mice and 10% of histones in humans are retained in sperm chromatin following the active exchange of histones with protamines (77,116). Importantly, retained histones have been mapped to regions of important developmental genes, suggesting that they designate those that are critical for postfertilization function in the zygote (117). As evidence to this point, disruption of the specific histone mark, H3K4me2, in sperm altered gene expression in the two-cell zygote and severely impaired offspring development (118). In addition, sperm from male rats that were administered chronic cocaine showed increased H3 acetylation specifically at the Bedn promoter in both paternal sperm and in the offspring brain, supporting the hypothesis that retained histone PTMs may denote genes important to offspring development (81,119). In addition to histone PTMs, protamine biochemical modifications have also been reported, supporting a potential protamine code in sperm that may impart transcriptional effects on embryo development (120). However, as protamines are rapidly replaced with maternal histones postfertilization (121), how such protamine modifications could influence embryogenesis requires further investigation.

CONCLUSIONS

The focus of stress as a risk factor for neuropsychiatric and neurodevelopmental disorders and the mounting evidence for the intergenerational transmission of parental stress exposure
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brings to light exciting new mechanisms involved in transmission of sex-specific stress signals. Many affected tissues are extraembryonic and easily accessible (e.g., placenta, semen), and thus the translational potential from animal models to prospective human studies may facilitate development of necessary predictive disease biomarkers. The potential to identify at-risk individuals may then inform clinical decisions, including altering prenatal care and earlier interventions for children. However, the discussion here only begins to appreciate the incredibly complex and multifaceted etiology that contributes to disease risk or resilience. Despite the growing evidence supporting intergenerational inheritance, there remains skepticism as to whether the transmission of parental experience is truly mediated by epigenetic mechanisms in the germ cell. For example, stress exposure may also impact offspring development via changes to parental care (e.g., maternal investment). Further, in paternal inheritance studies, the “sick sperm” hypothesis suggests that stress exposure can alter sperm maturation or motility and that offspring development may be affected by the integrity of fertilization or preimplantation events (122). Therefore, more studies with careful examination of these potentially complex factors are needed to determine the mechanism by which parental stress programs offspring development. Moreover, large prospective cohort studies in which gene × environment influences are considered, such as the National Institutes of Health–launched initiative Environmental Influences on Child Health Outcomes and the Avon Longitudinal Study of Parents and Children (123–125), will be invaluable to our ability to identify causal mechanisms as well as who may be at risk, and design prevention and therapeutic measures.

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ARTICLE INFORMATION

From the Department of Biomedical Sciences (JCC), School of Veterinary Medicine and Perelman School of Medicine University of Pennsylvania, Philadelphia, Pennsylvania; and the Department of Pharmacology (BMN, TLB), University of Maryland School of Medicine, University of Maryland, Baltimore, Maryland.

Address correspondence to Tracy L. Bale, Ph.D., Department of Pharmacology, University of Maryland School of Medicine, Howard Hall 403, 655 W Baltimore St, Baltimore, MD 21201; E-mail: tbleale@vet.upenn.edu.

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